# Should all men being evaluated for couple infertility have an endocrine and reproductive urology evaluation?

Although it is not currently standard care, the work by Trussell et al. in this issue of *Fertility and Sterility* suggests that endocrine and reproductive urology evaluation of male partners in infertile couples may provide useful insight as they demonstrate the importance of male testosterone levels for sperm morphology and live birth among couples seeking ovarian stimulation with the use of intrauterine insemination (1). Given the importance of characterizing the utility of a baseline work-up for all male partners seeking infertility care, we carefully evaluated the evidence presented here and note some key limitations and potential next steps as we seek to move research aims and clinical practice forward in this area.

First, only a marginal improvement in morphology was observed among men with testosterone >264 ng/dL. Given the variability in repeated semen analyses (2) and the poor association between semen parameters and live birth (3), it is not clear that this improvement is clinically meaningful. Furthermore, it remains unknown whether low testosterone truly does not influence the other semen quality parameters or whether the null findings in this study are in part an artifact of the eligibility criteria. Men had to have ≥5 million total motile sperm to participate, and so it is possible that low testosterone may be associated with other semen quality parameters among men with lower total motile sperm counts.

Second, notwithstanding the questions regarding the semen analysis parameters, the authors should be applauded for following the couples for pregnancy and live birth outcomes and evaluating associations of testosterone with live birth, the primary interest for couples seeking infertility care. This link between testosterone levels and live birth is especially intriguing in light of the need to identify potential opportunities for intervention to improve fertility and live birth rates. However, it is paramount to address the ever-present issue of confounding. Although the authors adjusted for age and body mass index, given their known associations with hormone levels and infertility treatment success, they were unable to account for potential medications that may play a role, such as clomiphene citrate, anastrazole, letrozole, hCG, and exogenous testosterone. Therapies to improve testosterone levels may be particularly relevant here because medical treatments may have been applied before the study measurement that influenced both the testosterone levels themselves and the success of the fertility treatments. These limitations are acknowledged in the discussion, though given the borderline associations with live birth it is important to understand whether these unmeasured factors could explain away the observed associations.

While it may seem that we are in a Catch-22 in needing to adjust for the unmeasurable, there are sensitivity analysis methods we can use to quantify whether these unmeasured factors would change our conclusions (in this case whether accounting for medications to improve low testosterone would make a difference) (4). The techniques are easy to implement and the benefits of knowing the potential implications of unmeasured confounding far outweigh the extra time and effort required to do the analysis. We posit that these techniques should become standard of practice in observational research to guide our interpretation of observational studies (4). We applied the sensitivity analysis techniques proposed by VanderWeele and Ding to the data presented in this paper (4), and found that the unmeasured confounder (medication use) would need to have an odds ratio of 1.9 with both the exposure (testosterone levels) and outcome (live birth) to fully explain away the association with live birth observed in this study. To bring the lower confidence limit to the null and make the finding statistically nonsignificant would require a confounder with an odds ratio of 1.0. Indeed, we do see that after the authors adjust for age and body mass index that the estimates are attenuated. Though it may be unlikely that the influence of medications would have such a strong effect to completely explain the findings and bring the point estimate to 1, it likely would attenuate the estimates to a small degree, and the conclusions should be interpreted accordingly.

Third, in thinking about the clinical implications of these results, we naturally wanted to know if there was a potential threshold level of testosterone that is needed and whether levels of other hormones may also be relevant. This study was limited in evaluating a single, and somewhat arbitrary, cutoff point for testosterone. A nod is given toward looking at other cutoff points in the future, though it is not clear why this was not fully explored in the present paper. This next step is needed to understand whether higher levels are also associated with reductions in morphology and live birth, and by how much. Furthermore, the conclusions drawn here are based on measurement of a single hormone, although we know that hormone levels are delicately interconnected and regulated. Typically, five to eight hormones are evaluated as part of a complete endocrinologic workup, and it would be helpful to understand more about the complete profile to put these results in context. Particularly in the setting of obesity, hyperestrogenism could also cause issues independently from low testosterone. Most importantly, perturbations in SHBG can significantly alter the bioavailable testosterone such that a man with a "normal" total testosterone level could have very low bioavailable testosterone. In addition, assessment of FSH and LH would identify men who had recently been on exogenous testosterone, were going into testicular failure, or had other forms of hypo- or hypergonadotrophic hypogonadism.

Overall, we agree that this study supports the rationale for baseline blood work-up for male partners as part of initial fertility evaluations. Indeed, many male partners of couples seeking infertility care would benefit from a more in-depth endocrinologic work-up and evaluation by a reproductive urologist regardless of semen parameters (2). Hormonal derangements identified and treated through referral to a reproductive urologist may enable more couples to conceive on their own or to have success with fertility treatments. The authors have made a significant contribution to the field that

underscores the importance of evaluating the male partner, and highlights that there may be actionable interventions for couples with unexplained infertility. Hormone interventions may be one option because they are typically simple and safe (although not Food and Drug Administration approved for this indication) and may provide a potential cost-saving option compared with assisted reproductive technologies. As such, this work is an important step toward advancing male reproductive health and couple-based outcomes, although it also shows that there is still much that is unknown in this area and we need to hold the bar of evidence high, especially as we seek to move the field forward in identifying potential targets for interventions to improve male fertility.

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